Advances in 3D-Printed Scaffolds for Spinal Cord Injury Repair

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Abstract. Spinal cord injury (SCI) is a type of central nervous system damage. Due to the limitations of current technologies in effectively reconstructing neural structures and restoring function in patients, there is an urgent clinical need for improved regenerative therapies. Against this backdrop, 3D-printed scaffold technology offers new possibilities for SCI repair by precisely simulating the complex three-dimensional structure of the spinal cord. The SCI repair scaffold system comprises three categories: axon-guiding, microenvironment-modulating, and neuron-replacing scaffolds, each repairing the nervous system through distinct pathways. Guiding scaffolds utilize micro topological structures to physically direct axonal growth, modulating scaffolds focus on restoring a healthy microenvironment to promote signal conduction, while replacing scaffolds leverage transplanted cells to directly facilitate synapse formation and neural circuit reconstruction. However, challenges such as low cell survival rates and imprecise microenvironment regulation persist, hindering further progress in 3D-printed scaffolds for SCI repair. This article reviews the application progress of 3D-printed scaffolds from the perspectives of structural guidance, microenvironment regulation, and cell replacement, aiming to provide references for research on spinal cord injury repair.

Keywords: 3D Printing scaffold, spinal cord, injury repair.

1. Introduction

As a form of central nervous system trauma, spinal cord injury (SCI) can persistently impair motor, sensory, and autonomic functions, leading to restricted mobility and reduced quality of life in patients [1]. The complexity of SCI repair lies in the fact that the initial mechanical injury triggers a cascade of subsequent reactions. Specifically, following vascular rupture, inflammation, and oxidative stress, the disease progression further manifests as inflammatory cell infiltration, reactive oxygen species accumulation, and glial scar formation. Although commonly used clinical treatments can partially stabilize the spine and alleviate symptoms, they struggle to effectively reverse neurological damage. The root cause lies in the inhibitory microenvironment-characterized by insufficient neurotrophic factors, accumulation of inflammatory cytokines, and upregulation of inhibitory molecules-along with glial scarring and disruption of neural signaling pathways, which collectively hinder the regeneration process. Therefore, there is an urgent clinical need to develop solutions that can delay the progression of SCI. Currently, significant progress has been made in the application of 3D printing technology to spinal cord injury treatment, primarily owing to its high-fidelity replication of spinal cord anatomical structures and biochemical characteristics. Researchers leverage this technology to address key challenges in the regeneration process, such as physical guidance, microenvironment regulation, and cellular integration.

Amid ongoing innovations in biomedical engineering methodologies, a growing body of research is focusing on three major categories of SCI repair scaffold systems. The first category, axon-guiding scaffolds, features oriented micro topological structures such as anisotropic fiber alignment and microchannel arrays, which provide directional pathways for axonal growth. To further enhance the guidance effect, anti-fibrotic agents such as RhoA/Rho kinase (ROCK) inhibitors or enzyme formulations released via degradable materials are integrated into the oriented fiber structures, aiming to simultaneously suppress astrocyte overactivation and scar formation [2]. The second category, termed microenvironment-modulating scaffolds, employs a repair strategy centered on reconstructing the electrophysiological microenvironment and providing neurotrophic support. Researchers commonly use bio-conductive materials such as conductive hydrogels and graphene to mimic the electrical conductivity of neural tissues. To reconstruct damaged neural circuits, these conductive

materials are loaded with neurotrophic or anti-inflammatory factors, offering nutritional support for signal transmission in the injured area, as well as for myelination regeneration, synapse formation, and angiogenesis [3]. The third category, neuron-replacing scaffolds, utilizes bioinks as their material foundation. These bioinks possess properties akin to the natural extracellular matrix (ECM), providing cell adhesion interfaces and ensuring biomechanical support. Functioning as a bioactive platform, this scaffold category offers a cytocompatibility biomimetic microenvironment to ensure the survival, directed differentiation, and tissue integration of implanted cells. Building on this foundation, genetically engineered cells or induced pluripotent stem cell (iPSC)-derived neurons interact with the scaffold, ultimately working synergistically to promote angiogenesis and reconstruct neural function [4]. Currently, existing technologies still face numerous challenges: complex printing processes and cumbersome operations; limitations of bioinks in terms of mechanical properties, bioactivity, and degradation rates. Also, insufficient precision in simulating complex pathological microenvironments; and the need for further validation of long-term safety and functional regeneration outcomes are important directions that needs to be explored.

This article outlines the pathophysiological characteristics of SCI and the application advantages of 3D-bioprinted scaffolds, also providing a detailed discussion of the design principles, present research progress, and therapeutic limitations of the aforementioned three scaffold types. It seeks to guide the improvement of current scaffolds and the creation of new ones, paving the way for novel therapies and hope for spinal cord injury patients.

2. Pathology and Repair of Spinal Cord Injury

Spinal cord injury is a pathological condition that can severely affect the central nervous system and often leads to high rates of disability (Fig. 1). It can be classified into traumatic injuries caused by falls, sharp force trauma, etc., and non-traumatic injuries resulting from congenital spinal cord developmental disorders or acquired spinal cord pathologies [5].

Spinal cord injury pathology exhibits characteristics of progressive damage expansion, divided into four stages. The acute phase (<48 h) is dominated by blood-spinal cord barrier disruption, hemorrhage, and ischemia. The subacute phase (weeks) involves edema and pro-inflammatory factor release, accompanied by calcium overload and mitochondrial dysfunction leading to apoptosis; the chronic phase (>6 months) shows vascular regeneration and neural remodeling, but apoptotic cells combined with an inhibitory microenvironment ultimately develop into a cavity surrounded by scars [6].

For spinal cord injury, although a range of therapeutic strategies have been developed, including surgical decompression, pharmacological therapy, and neural regenerative cell-based technologies [7], the presence of post-injury inflammatory responses and scar tissue results in low survival rates of implanted cells and inhibited growth of regenerating axons [8]. Complete functional recovery remains challenging [9], highlighting the urgent need for improved regenerative therapies to treat spinal cord injury.

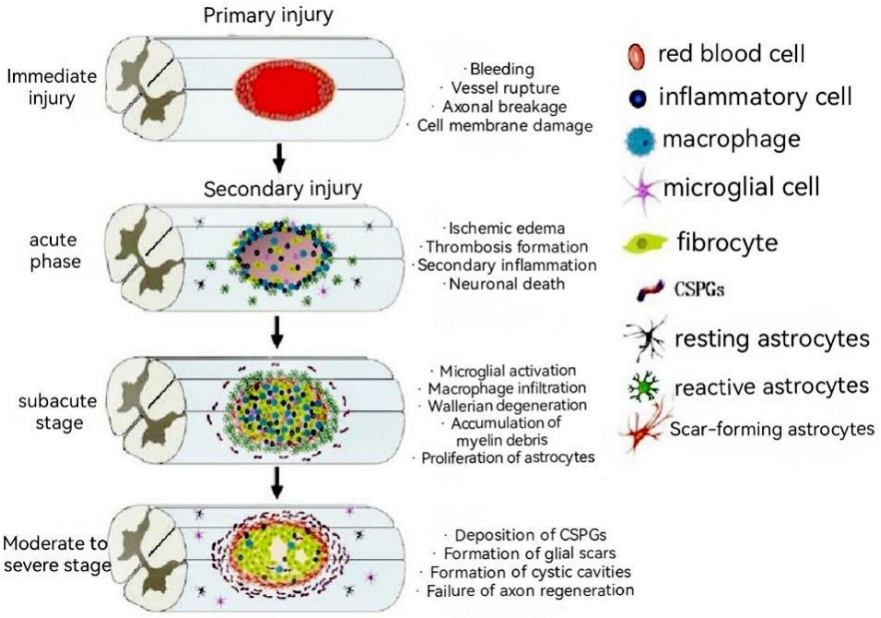

Figure 1. Pathological process of spinal cord injury [10]

3. Principles of Functional 3D-Printed Scaffolds

Three-dimensional scaffolds prepared by traditional tissue engineering techniques (freeze-drying, electrospinning, melt molding, etc.) cannot be designed with internal structures, have uncontrollable porosity, and fail to accurately simulate the intricate internal architecture of biological tissues. In contrast, 3D-printed bionic scaffolds utilize biomolecular materials notably collagen [11]. Based on structural scan data of the injury site, a specific spinal scaffold model is designed. This enables the production of spinal scaffolds that meets implantation requirements in terms of shape, size, and complete internal structure. During implantation at the injury site, these scaffolds allow for orientation assessment and precise integration, facilitating repair and regeneration of the damaged area (Fig. 2).

3D-printed scaffolds are capable for serving both as contact guidance for axonal regeneration in the injured area and serve as carriers for delivering stem cells, thereby altering the microenvironment that is unfavorable for neural regeneration. Therefore, 3D-printed bionic scaffolds possess inherent advantages in comprehensive SCI treatment.

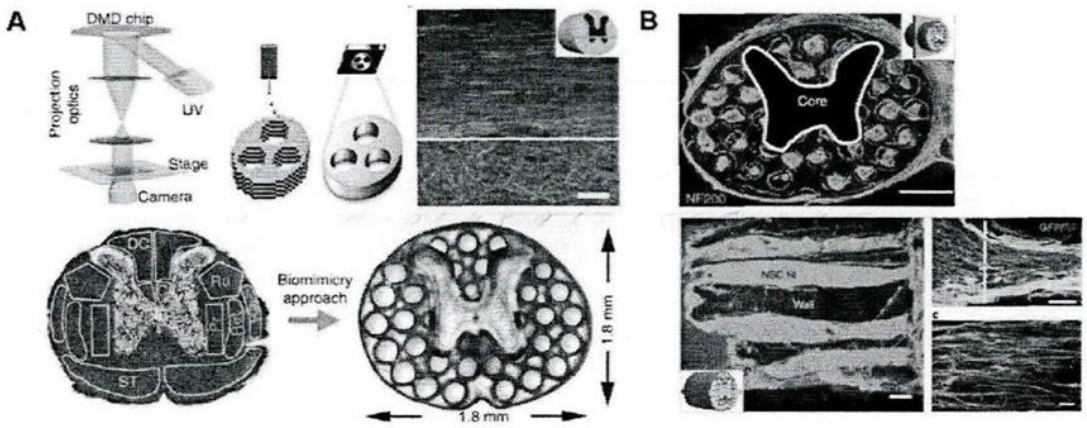

Figure 2. A Fabrication of bionic neural tissue scaffolds mimicking spinal cord organizational structure **B** Neural regeneration following in vivo transplantation of bionic neural tissue scaffolds [12]

4. Classification and Construction of Scaffold Systems

The core objective of 3D-printed scaffolds is to overcome natural repair barriers in SCI-such as structural obstruction, cell loss, inhibitory microenvironment, and abnormal electrical signaling. Through engineering approaches, ultimately achieving neural functional reconstruction. Existing scaffolds can be functionally categorized into three major systems: axon-guiding, microenvironment-modulating, and neuron-replacing types. These scaffolds integrate structural support, cell therapy, and biochemical regulation, potentially promoting axonal regeneration, synaptic reconstruction, and functional recovery, ultimately achieving more efficient tissue reconstruction than natural repair.

4.1. Axon-Guiding Scaffolds: Structural Bridging

Axon-guiding scaffolds are 3D-printed scaffolds devoid of living cells. They achieve structural replication of the natural spinal ECM topology through precisely aligned microfibers, providing continuous growth pathways for axonal extension and serving a structural bridging function. However, a scaffold design confined to providing structural guidance for axonal growth, is incapable of promptly reparing or replenishing the lost neural cells within the spinal cord lesion. To maximally ameliorate motor dysfunction resulting from spinal cord injury, cells or neurotrophic factors can be integrated with 3D-printed scaffolds as needed.

For example, using three-dimensional printing technology, Joung et al. implanted two types of iPSC-derived cells into distinct layers of a multichannel scaffold, enabling their proliferation and differentiation within the scaffold to form neurons and oligodendrocytes. This approach contributes to the reconstruction of functional axonal connections in the injured area, thereby repairing central nervous system (CNS) tissue [13]. Li Zhixiang et al. combined paclitaxel-loaded nanoparticles (PTX-NPs) with serine methacrylamide (SilMA) hydrogel. Paclitaxel (PTX) promotes the differentiation of neural stem cells toward neurons via the MAPK/ERK signaling pathway, while concurrently suppressing their proliferation into astrocytes (Fig. 3). The elastic modulus of the scaffold matches that of neural tissue, providing an ideal scaffold microenvironment to reduce pathological ECM deposition and thereby minimize fibrous scarring [14].

Such scaffolds can address the challenge of overcoming physical barriers after spinal cord injury and reduce scar formation. Astrocytes in the spinal cord form scar tissue after injury, shown in Fig. 4 [15]. This structure has a dual effect: on one hand, it shields local inflammation and provides protection to adjacent tissues; on the other hand, the inhibitory effect of the regenerative barrier it creates is more prominent, ultimately limiting axonal regeneration. Therefore, reducing scar tissue and providing essential support and guidance cues for the extension of regenerating axons are critical for neural regeneration.

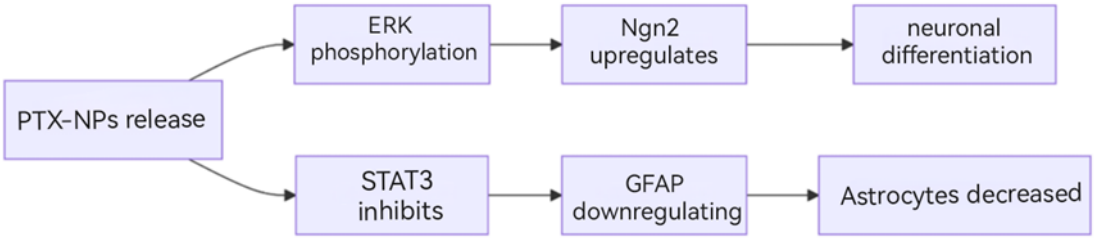

Figure 3. Picture credit : Original

Note: Ngn2 - Neurogenin 2 | STAT3 - Signal Transducer and Activator of Transcription 3 | GFAP - Glial Fibrillary Acidic Protein,Two distinct strategies for 3D-printed axon-guiding scaffolds

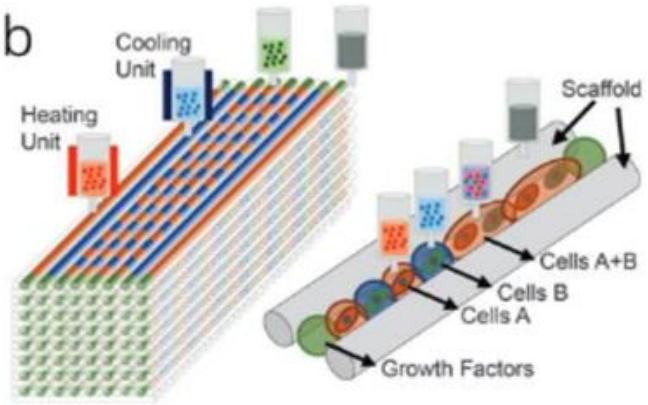

Figure 4. Alginate hydrogel scaffolds for spinal cord repair [15]

4.2. Microenvironment-Modulating Scaffolds: Electrical Stimulation + Biofactor Delivery

Electrical signaling is a key physiological element regulating cellular behavior and achieving functional integration. To better restore neural conduction function, researchers have proposed microenvironment-modulating scaffolds capable of delivering electrical stimulation (ES) [16]. This category of scaffolds consists of 3D-printed structures that combine conductive materials with growth factors (Fig. 5). The electroactive biomaterials within them possess the ability to establish conductive pathways and create a microenvironment at the injury site resembling that of natural spinal cord regeneration. This promotes neuronal and synaptic regeneration, thereby restoring neural conduction function in damaged pathways [17]. Meanwhile, growth factors facilitate cell proliferation, migration, differentiation, and angiogenesis, while also exhibiting anti-apoptotic, antioxidant, and immunomodulatory properties [18, 19].

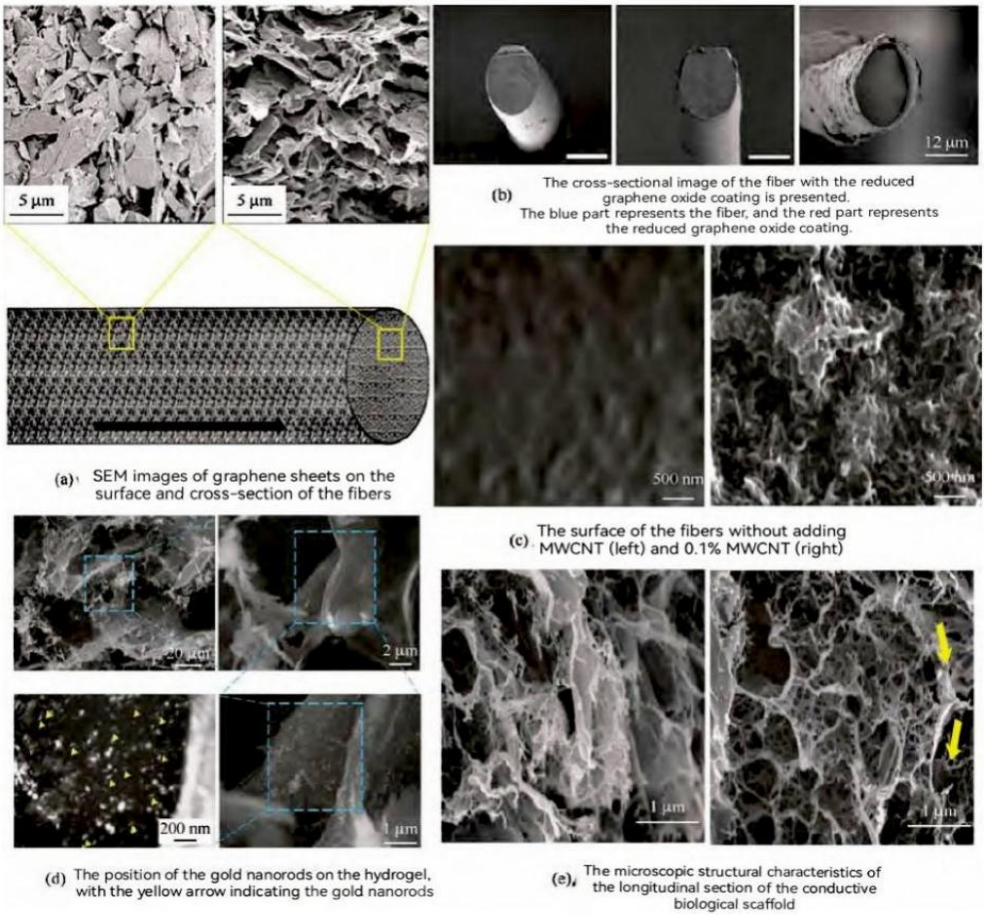

Figure 5. Microstructural images of scaffolds with different conductive materials [20]

Microenvironment-modulating scaffolds utilize conductive materials to promote the controlled release of growth factors, optimize the electrochemical microenvironment conducive to tissue repair, and reconstruct electrical signal transmission [21], stimulating the directional differentiation of oligodendrocytes and promoting myelination regeneration. Conductive materials loaded with cytokines exhibit an electrical stimulation synergistic effect in vivo: external electrical stimulation activates ion channels, increases Ca^{2+} influx, and promotes neurotrophic factor secretion to regulate myelin-related gene transcription (Fig. 6).

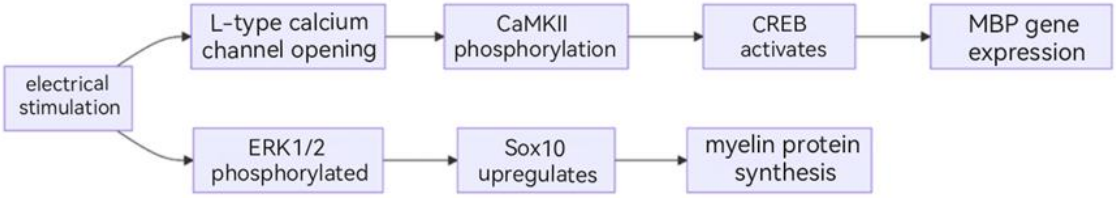

Figure 6. Mechanism of Electrical Stimulation Promoting Myelination Regeneration

Note: CaMKII - Calcium/Calmodulin-Dependent Protein Kinase II | CREB - cAMP Response Element-Binding Protein | MBP - Myelin Basic Protein | ERK1/2 - Extracellular Signal-Regulated Kinase 1/2 | Sox - Transcription Factor

4.3. Neuron-Replacing Scaffolds: Cell Carriers

Neural stem cells (NSCs) possess multipotent differentiation capabilities into neurons and glial cells, enabling the reconstruction of neural cells at the injury site. Their implantation holds significant application value in SCI treatment. Evidence has confirmed that NSC transplantation can fill lesion cavities and promote structural repair, facilitating neural and vascular regeneration while providing trophic support. With anti-inflammatory and anti-apoptotic effects, it represents a potent potential strategy for enhancing neurological functional recovery after SCI [22].

However, due to cerebrospinal fluid circulation, implanted stem cells are prone to disperse through blood flow, significantly compromising their therapeutic efficacy [23]. Hydrogels can serve as delivery systems for stem cells, efficiently targeting them to the lesion area. This approach not only significantly reduces cell loss but also provides a three-dimensional microenvironment conducive to cell colonization, expansion, and differentiation. For example, to construct acellularized scaffolds, Liu et al. designed a sodium alginate/gelatin bioink incorporating oligodendrocytes and NSCs, which was printed into a hydrogel structure [24]. This scaffold facilitates the myelination process of axons, thereby accelerating the recovery of hindlimb motor function in model rats. Gu Wenbo et al. utilized genetic engineering techniques to construct NEP1-40 gene lentiviral transfection of NSCs and co-cultured them with hyaluronic acid (HA) hydrogel scaffolds to provide a suitable microenvironment for NSC growth and differentiation. This approach overcomes the inhibitory effects of factors at the spinal cord injury site, promotes neuronal axon growth and extension, and guides neural connections to facilitate neural repair [4].

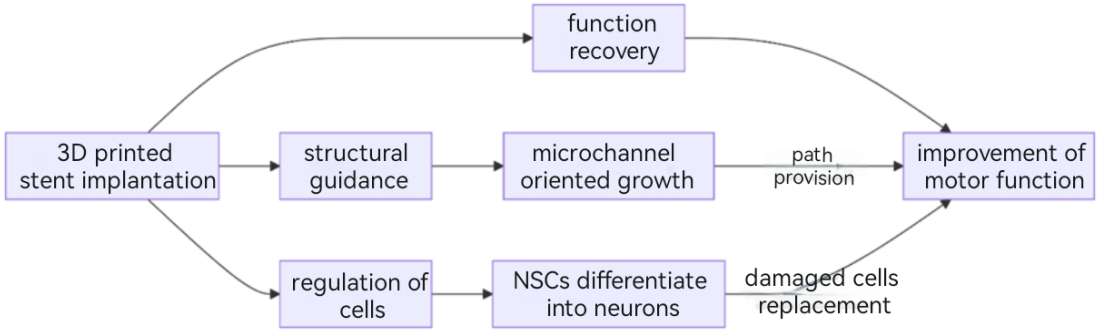

Figure 7. Pathway of neuron-replacing scaffolds improving motor function

This type of scaffold establishes a platform for promoting neuronal regeneration at spinal cord lesion sites. The oriented microchannel topological structure guides the orderly growth and

arrangement of NSCs, while synergizing with genetically modified NSCs to promote neuronal differentiation and suppress astrocyte formation, thereby inhibiting glial scar development. Building on this, some scholars propose that utilizing neurotrophic factors can provide a more substantial driving force for the survival, development, and differentiation of neural cells (Fig. 7) [25].

5. Challenges and Prospects

Despite the significant potential demonstrated by 3D printing technology in SCI repair, it still faces major challenges in spinal cord injury applications. The first challenge is that existing bioinks struggle to balance printability, biocompatibility, and mechanical properties, while lacking sufficient mechanical strength and stability to meet the mechanical, rheological, and biological demands of the injury site. Secondly, existing bioprinting technologies have limitations in structurally mimicking the complex neuronal networks and heterogeneous cell distribution of the spinal cord. This results in constructed scaffold microenvironments tending to be homogeneous, far from resembling the ECM, and incapable of achieving zonal regulation of cells and active factors. Consequently, their application in the field of SCI is significantly constrained. The key to future research lies in ensuring material biocompatibility, optimizing manufacturing processes, and validating their efficacy in promoting neural functional reconstruction. Moreover, the application in the field of SCI is highly limited. Future research should prioritize optimizing these technologies for clinical use, emphasizing safety, scalability, and efficacy.

Notstanding, it must be emphasized that the most advanced spinal cord repair scaffolds are integrated systems combining the three aforementioned functional types-referred to as "all-in-one" or "multifunctional" scaffolds. An ideal design might consist of a biodegradable structural scaffold with oriented microchannels, internally loaded with neurotrophic factors, and pre-seeded with neural stem cells within its pores. This multifunctional synergistic strategy, intervening simultaneously at the physical, chemical, and biological levels, may represent the most promising direction for achieving effective repair of spinal cord injury.

6. Conclusion

This article primarily introduces current research on the application of commonly used 3D-printed scaffolds, covering scaffold systems including: axon-guiding, microenvironment-modulating, and neuron-replacing types. Additionally, it elaborates on the construction principles and research objectives of these three major scaffold systems. Overall, 3D-printed scaffold technology offers an engineered strategy for spinal cord injury repair characterized by high structural adaptability and functional diversity.

The field still faces critical bottlenecks such as insufficient mechanical properties of bioinks, limited biomimetic complexity of microenvironments, and low survival rates of transplanted cells. Future efforts should focus on developing integrated intelligent scaffolds that incorporate multimodal bio fabrication strategies to synergistically regulate the SCI repair process, thereby achieving neural regeneration and functional recovery. This article explores the repair mechanisms and application prospects of 3D-printed scaffolds in SCI, aiming to contribute to subsequent research in related fields.

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